Cancer Chemother Pharmacol (1993) 33: 139–143

Cancer Chemotherapy and Pharmacology

A phase I trial of high-dose continuous-infusion hydroxyurea

David C. Smith[1*], William P. Vaughan[3], Peter R. Gwilt[4], and Donald L. Trump,[1,2*]**

[1] Division of Hematology/Oncology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA
[2] Duke Comprehensive Cancer Center, Durham, North Carolina, USA
[3] College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA
[4] College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, USA

Received: 7 April 1993 / Accepted: 22 July 1993

Abstract. Hydroxyurea inhibits ribonucleotide reductase, resulting in depletion of intracellular deoxynucleotide pools and inhibition of DNA repair. It has been used in a variety of malignancies and is usually given orally. Deoxynucleotide depletion is directly related to the concentration of and duration of exposure to hydroxyurea; thus, prolonged continuous infusion may result in increased therapeutic efficacy. A total of 30 patients were treated on this trial, designed to determine the maximum tolerated doses (MTD) of intravenous hydroxyurea given as a 24- or 48-h continuous infusion. The MTD for the 24-h infusion was 13,520 mg/m^2 following a bolus of 1,690 mg/m^2, and the mean ($\pm$ SD) plasma steady-state concentration was 1.93 $\pm$ 0.52 mM. For the 48-h infusion, the MTD was 17,576 mg/m^2 following a bolus of 2,197 mg/m^2 and the mean steady-state level was 1.43 $\pm$ 0.31 mM. The dose-limiting toxicity on both schedules was marrow suppression manifesting as neutropenia and thrombocytopenia. Pharmacokinetic analysis revealed decreasing clearance with increasing dose, implying that drug elimination is saturable. Pharmacodynamic analysis showed a slight correlation between steady-state plasma levels and the degree of marrow suppression.

This work was supported in part by grants 5T32-CA-09307, P30-A-14236-18, and 5-R01-CA45529 from the National Institutes of Health and the National Cancer Institute and by the P.B. Cohen Memorial Fund

* *Present address:* Pittsburgh Cancer Institute, Division of Medical Oncology, 3459 5th Avenue, 7 Main North, Pittsburgh, PA 15213, USA

** *Present address:* University of Alabama-Birmingham, School of Medicine, 1900 University Boulevard, THT 513, Birmingham, Alabama, USA

Correspondence to: David C. Smith, Pittsburgh Cancer Institute, Division of Medical Oncology, 3459 5th Avenue, 7 Main North, Pittsburgh, PA 15213, USA

Introduction

Hydroxyurea selectively kills cells in the S-phase of the cell cycle by binding to and inhibiting the M2 subunit of ribonucleotide reductase [1]. This enzyme catalyzes the rate-limiting step of de novo deoxynucleotide triphosphate synthesis [9]. Its inhibition results in depletion of intracellular deoxynucleotide pools and impairment of DNA synthesis and repair [6, 21]. The depletion of deoxynucleotide pools and the cytotoxicity of hydroxyurea are correlated with both the duration of exposure and the concentration achieved [11, 15].

Hydroxyurea is usually given orally. When delivered via this route it is rapidly absorbed, showing significant interpatient variability in serum levels [5, 18]. Since hydroxyurea-induced depletion of nucleotide pools is dependent on both the concentration and the duration of exposure and the drug's cytotoxicity is S-phase-specific, oral administration of hydroxyurea requires multiple daily dosing for maximal clinical effect. In view of the rapid elimination, need for frequent dosing, and interpatient variability in levels, consistent achievement of optimal plasma levels is limited. The effects in terms of inhibition of repair, potentiation of cytotoxicity, and direct cytotoxicity are therefore highly variable.

Intravenous administration addresses this problem of inconsistent drug delivery, and continuous infusion can provide a long duration of exposure at relatively high concentrations. Continuous infusion of hydroxyurea has been studied in three trials [5, 7, 22] and is feasible, but carefully conducted phase I trials of intravenous hydroxyurea are limited in number and scope. These trials demonstrated that steady-state concentrations of hydroxyurea could be reached within 1 h following a loading dose [5] and that a concentration of 1 mM could be achieved [22]. Despite these efforts, the maximum tolerated doses (MTDs) of hydroxyurea given as a continuous infusion over 24 and 48 h are not known. We therefore undertook a phase I trial of continuous infusion hydroxyurea to determine the MTD of hydroxyurea given as a 24- and 48-h continuous infusion. We also sought to describe more fully the toxicity

associated with high-dose continuous infusion, to determine the steady-state plasma concentrations in patients on these regimens, and to explore pharmacodynamic relationships between the steady-state concentration and the toxicity, particularly myelosuppression.

Patients and methods

Patients. From January 31, 1990, through August 13, 1991, 30 patients with refractory advanced malignancies were enrolled and treated on this study at Duke University Medical Center. Eligible patients were required to be at least 18 years of age and to have a histologic diagnosis of malignancy, an Eastern Cooperative Oncology Group performance status of ≤ 2, and adequate hematopoietic [absolute neutrophil count (ANC), $\geq 1{,}500$/ml; platelet count, $\geq 100{,}000$/ml], hepatic [total bilirubin, ≤ 2.0 mg/dl, aspartate amino transferase (AST), ≤ 4 times the standard value], and renal (creatine, ≤ 2.0 mg/dl) function. Prior chemotherapy must have been completed at least 3 weeks before study entry (6 weeks for mitomycin C and nitrosoureas). Measurable disease was not required. The study protocol was approved by the Institutional Review Board of Duke University Medical Center and written informed consent was obtained from all patients.

Pretreatment evaluation and follow-up studies. Prior to study entry and to each treatment, all patients underwent a complete physical examination and a laboratory evaluation consisting of a complete blood count (CBC); determinations of prothrombin time, activated partial thromboplastin time, serum electrolytes, calcium, phosphorus, uric acid, alkaline phosphatase, AST, lactate dehydrogenase (LDH), and bilirubin; urinalysis; and 24-h urine collection for evaluation of creatinine clearance. A CBC and differential count as well as determinations of creatinine, alkaline phosphatase, bilirubin, and AST were obtained weekly during the study period. Tumor assessment was obtained prior to each treatment cycle. Standard criteria for response were employed.

Drug administration and dose. Hydroxyurea was supplied by Bristol-Myers/Squibb in 50-ml vials, each containing 2 g of hydroxyurea. Each vial was reconstituted with 18.5 ml of sterile sodium chloride or 5% dextrose water and was then further diluted to the appropriate concentration in 1 l of normal saline.

Hydroxyurea was given as an intravenous loading dose over 30 min followed by a continuous 24-h intravenous infusion. The loading dose at each dose level was equivalent to 3 times the amount infused over 1 h during the continuous infusion. This schedule has been demonstrated to result in steady-state concentrations of hydroxyurea within the 1st h of drug administration [5]. The initial loading dose was 600 mg/m^2 with a continuous infusion of 4,800 mg/ m^2/ 24 h[1]. This dose was derived from the previously published experience with continuous-infusion hydroxyurea [5] and the experience with patients treated at this dose on a separate trial (WP. Vaughan, unpublished data).

Subsequent dose escalations were carried out in increments of 30%. Three patients were treated at each dose level. If $\geq$ grade 3 (National Cancer Institute Common Toxicity Criteria) toxicity in any organ system was seen in one or more patients at a given dose level, at least three additional patients were enrolled at that level for a better definition of the toxicity. When reversible dose-limiting toxicity ($\geq$ grade 3, DLT) occurred in at least three of six patients enrolled at a dose level, dose escalation was discontinued. The MTD was defined as the dose one level below that at which DLT occurred. When the MTD for a 24-h infusion had been defined, an additional three patients were enrolled, with the duration of the infusion being increased to 48 h. The initial dose for the 48-h infusion was the dose at which DLT was seen following the 24-h infusion. The dose was then escalated in increments of 30% until the criteria for definition of the MTD were met. Only data from the first cycle of therapy were utilized to define the MTD.

Treatment was repeated every 4 weeks until there was evidence of disease progression or intolerable toxicity. Patients who had completed a full 28-day evaluation cycle with no toxicity of > grade 1 were eligible to receive additional cycles at the next dose level, provided that at least two patients had received the higher dose and had developed no toxicity of > grade 2 after at least 2 weeks of observation. In patients with toxicity, therapy was delayed until laboratory values had returned to levels consistent with the entry criteria for the study. Subsequent doses were reduced by 30% for any patient with $\geq$ grade 3 nonhematologic toxicity (other than nausea, vomiting, diarrhea, or headache occurring during the continuous infusion) or grade 4 hematologic toxicity.

Table 1. Patients characteristics

Number of patients	30
Sex (M/F)	18/12
Median age (range)	61.5 (31 – 75 years)
Disease site:	
Head and neck	11
Colorectal	7
Lung (NSC)	3
Ovarian	2
Other[a]	7
Prior therapy:	
Chemotherapy	28 (median, 3 prior regimens)
Radiation	19
Hormonal	2

NSC; Non-small-cell

[a] One of each of the following: adenocarcinoma of the prostate, breast, gallbladder, and unknown primary; adenoid cystic carcinoma; squamous-cell carcinoma of the skin; and leiomyosarcoma

Hydroxyurea assay. Blood samples were obtained in heparinized tubes immediately following completion of the loading dose and at 15 and 30 min as well as 4, 8, 16, 20, and 24 h following the loading dose on the 24-h infusion schedule. Additional specimens were obtained at 28, 32, 36, 40, 44, and 48 h following the loading dose on the 48-h infusion schedule. Samples were immediately centrifuged and the plasma was separated and frozen at ≤ 4°C until analyzed. Hydroxyurea was assayed by the method of Fabricius and Rajewsky [10]. After thawing, the plasma was deproteinated with perchloric acid, centrifuged, and filtered. The filtrate was treated with iodine to oxidize the hydroxyurea. The nitrate formed by this reaction diazotizes sulfanilic acid, which then couples with *N*-(1-naphthyl)-ethylenediamine dihydrochloride. The coupled product absorbs ultraviolet light at 540 nm.

Pharmacokinetics studies. The plasma hydroxyurea concentration-time data were analyzed using the computer software package NONMEM (version III) and the PREDPP package (version II) [3, 4]. The data were fit to a one-compartment model with Michaelis-Menten elimination and first-order renal excretion as described by the equation:

$$\frac{dC}{dt} = \frac{V_{max}C}{K_M + C} - K_eC,$$

where the rate of change in drug concentration in the plasma is denoted by dC/dt, V_{max} is the maximal elimination rate by the nonlinear route, K_M is the Michaelis constant for hydroxyurea elimination, and the first-order rate constant is denoted by K_e.

Results

The characteristics of the 30 patients treated on this trial are summarized in Table 1. Most patients were heavily pretreated, with a majority having had both chemotherapy and radiation for their disease. A total of 20 patients were

Table 2. Hydroxyurea: hematologic toxicity after a 24-h infusion

Dose: bolus/CI (mg/m^2)	Number of patients	Toxicity grade (WBC/Plt/Hb)			
		1	2	3	4
600/4,800	3	0/0/0	0/0/0	0/0/0	0/0/0
780/6,240	4[a]	0/0/0	0/0/0	0/0/0	0/0/0
1,000/8,000	2	0/1/0	1/0/1	0/0/0	0/0/0
1,300/10,400	3	2/0/0	1/2/1	0/0/0	0/0/0
1,690/13,520	3	1/0/1	1/0/0	1/0/0	0/0/0
2,197/17,576	5	0/1/1	0/0/2	3/3/1	2/0/0

CI, Continuous infusion; WBC, white blood count; Plt, platelets; Hb, hemoglobin

[a] One patient not evaluable due to insufficient data

Table 3. Hydroxyurea: hematologic toxicity after a 48-h infusion

Dose: bolus/CI (mg/m^2)	Number of patients	Toxicity grade (WBC/Plt/Hb)			
		1	2	3	4
2,197/17,576	6	1/0/4	3/0/0	1/0/1	1/0/0
2,856/22,849	4	0/2/3	1/0/1	1/1/0	2/0/0

CI, Continuous infusion; WBC, white blood count; Plt, platelets; Hb, hemoglobin

treated on the 24-h infusion schedule. The total number of courses of therapy delivered via 24-h infusion was 44, with a median of 2 courses being given (range 1–7). Eight patients were treated at two dose levels: six with dose escalations after minimal toxicity and two with dose reductions after neutropenia. An additional two patients were treated at three dose levels, both with dose escalations following minimal toxicity at their two earlier dose levels. Ten patients were treated on the 48-h infusion schedule. A total of 25 courses were delivered via 48-h infusion, with a median of 2 courses being given (range, 1–5). Five patients were treated at two dose levels and one was treated at three levels: two patients had dose escalation following minimal toxicity, and four (including the patient treated at three levels) required dose reduction for toxicity.

Tables 2 and 3 summarize the number of patients treated and the hematologic toxicity recorded at each dose level on the first course. One patient treated at the second dose level was not evaluable for toxicity due to his failure to have his weekly laboratory tests drawn. He was subsequently retreated without incident. Only two patients were treated at the third dose level (bolus, 1,000 mg/m^2; infusion, 8,000 mg/m^2) due to an interruption in the drug supply. Patient accrual was halted so as to ensure that patients who had been enrolled could receive at least two courses of therapy. All four patients on the previous level (bolus, 780 mg/m^2; infusion, 6,240 mg/m^2) were escalated to this dose without developing toxicity; thus, when intravenous hydroxyurea was again available, patient accrual was continued at the next dose level (bolus, 1,300 mg/m^2; infusion, 10,400 mg/m^2).

As expected, the principal toxicity associated with continuous-infusion hydroxyurea was myelosuppression manifesting as neutropenia and thrombocytopenia. Although somewhat variable, nadir counts were usually seen on day 8, with recovery being noted by day 14 on the 24-h infusion schedule. One heavily pretreated patient consistently had his lowest counts recorded on day 22, with recovery ocurring by day 28. On the 48-h infusion schedule, the myelosuppression was again seen by day 8, but nadir counts were more often recorded on day 15, suggesting that the period of myelosuppression may have been prolonged with the increased duration of infusion. There was no delay in therapy due to persistent myelosuppression, and all patients who were eligible for continued therapy received their next course on schedule. There was no evidence of cumulative toxicity in those patients capable of receiving multiple cycles of therapy.

On the 24-h schedule a single episode of grade 3 neutropenia was seen in a patient treated at a bolus dose of 1,690 mg/m^2 followed by 13,520 mg/m^2 as a continuous infusion. This occurred in a heavily pretreated patient. The other two patients on this cohort, both of whom had also been pretreated, received multiple cycles of therapy without showing evidence of toxicity. Additional patients were not enrolled at this level and escalation was continued. Dose-limiting myelosuppression was encountered at the next dose level (bolus, 2,197 mg/m^2; continuous infusion, 17,576 mg/m^2). Grade 3 leukopenia and thrombocytopenia were seen in three of five patients treated at this dose level. Mild to moderate anemia was also documented in patients treated at this dose level, and one patient required transfusion. No patient required platelet transfusion. The MTD for the 24-h schedule was thus a bolus of 1,690 mg/m^2 with an infusion of 13,520 mg/m^2. The median ANC nadir at the MTD was 1300/μl (range, 700–2,600/μl) and the median platelet nadir was 164,000/μl (range, 140,000–231,000/μl). The mean steady-state plasma concentration of hydroxyurea at the MTD was 1.93 ± 0.52 m*M*.

On the 48-h schedule, at a bolus dose of 2,197 mg/m^2 and continuous infusion of 17,576 mg/m^2, grade 4 neutropenia was seen in two of six patients, with one of these having a grade 3 anemia. A third patient in this cohort had neutropenia at the borderline for grade 3. This dose proved to be the MTD for the 48-h schedule, as toxicity was dose-limiting at the next level (bolus, 2,856 mg/m^2; continuous infusion, 22,849 mg/m^2). Two of four patients treated at this level developed grade 4 leukopenia, and a third had grade 3. Nine of the ten patients treated on this schedule developed mild to moderate anemia, but only one required transfusion. None of these patients were symptomatic or required hospitalization due to anemia. The median ANC nadir at the MTD was 1080/μl (range, 30–1,568/μl) and the median platelet nadir was 176,000/μl (range, 84,000–324,000/μl). The mean steady-state plasma concentration of hydroxyurea at the MTD on the 48-h infusion was 1.43 ± 0.31 m*M*.

Two patients died during the course of this trial. In both cases this was due to rapid progression of their malignant disease. In neither of these cases was toxicity from hydroxyurea felt to be a contributing factor. One patient was hospitalized with febrile neutropenia following his third cycle of therapy at a reduced dose. This was the only episode of febrile neutropenia during this trial, although two other patients were treated with antibiotics during their

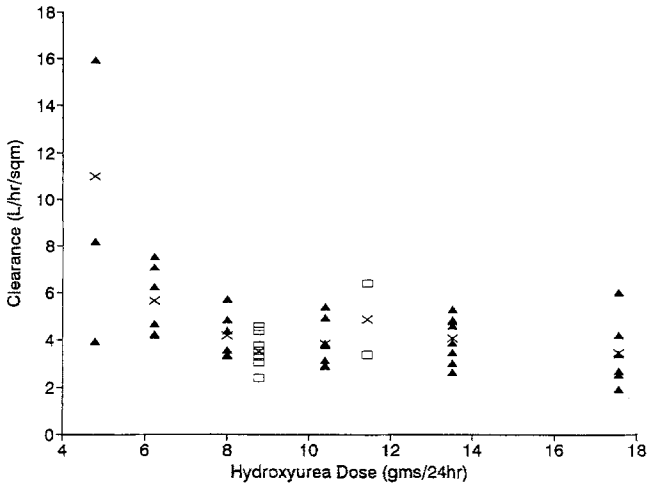

Fig. 1. Total body clearance of hydroxyurea. □, 48-h-infusion; ▲ , 24-h-infusion; ×, mean value

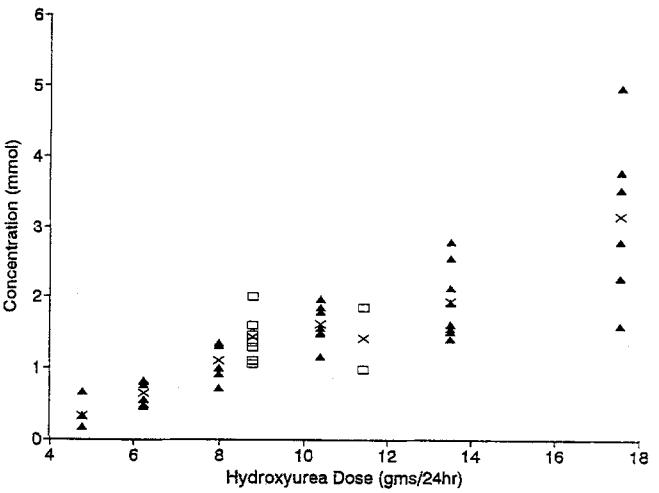

Fig. 2. Steady-state plasma concentrations of hydroxyurea. □, 48-h-infusion; ▲ , 24-h-infusion; ×, mean value

nadirs by their local physicians. The other toxicities seen on this trial were mild. Five of the ten patients treated on the 48-h infusion schedule developed an erythematous, pruritic, whole body rash. The rash was transient and required therapy with antihistamines and steroids in only one patient. There was no desquamation seen. One patient developed acute polyarthritis following her fourth course of hydroxyurea. Rheumatologic evaluation showed a positive antinuclear antibody and rheumatoid factor but no specific etiology for her arthritis. She was treated with steroids and experienced complete resolution of her joint pain and swelling, but refused further therapy with hydroxyurea. One patient developed transient grade 1–2 mucositis on the 48-h infusion schedule at the highest dose level, which resolved spontaneously and did not recur with further therapy.

No response was seen in the patients with measurable or evaluable disease. The median duration of therapy was 2 months. Therapy was discontinued in 21 patients due to progression of their disease, because of toxicity in 1 subject (the patient with arthritis), at the request of 1 patient (without documented toxicity or progression), and 2 subjects died during treatment. Therapy was limited in the remaining five patients due to an interruption in the drug supply. These patients were offered alternative therapy including oral hydroxyurea.

The pharmacokinetics of hydroxyurea were consistent with elimination by parallel nonlinear and linear pathways. The nonlinear route was presumably liver metabolism and could be adequately described by the Michaelis-Menten equation (see above), where the population mean value of V_{max} = 3.40 mmol/h and K_m = 0.21 m*M*. The linear pathway, apparently renal excretion, was characterized by a population mean renal clearance of 3.64 l/h, that is, approximately 75% of the normal glomerular filtration rate. The volume of distribution was 38.1 l, equivalent to total body water.

The effect of these parallel paths of elimination is demonstrated in Fig. 1. The total body clearance at low doses was significantly greater than that at high doses due to saturation of the nonlinear pathway. Analysis of the steady-state plasma hydroxyurea levels, shown in Fig. 2, revealed a disproportionate increase in concentration with dose. A detailed description of the pharmacokinetic analysis of hydroxyurea applied in this study has been presented elsewhere (Tracewell et al., submitted for publication.)

There was little interpatient variability in either steady-state concentration or clearance across most dose levels as demonstrated in Figs. 1 and 2. The exceptions occurred in the steady-state levels at the highest delivered dose (sample SD, 1.21 m*M*) and in the clearance at the lowest dose level (sample SD, 5.96 l/ h^{-1}/ m^{-2}). The latter observation is accounted for by two patients whose plasma levels of hydroxyurea were at or just below the standard range for the hydroxyurea assay employed, implying that the clearance at this lowest dose level may actually be higher than the reported value.

Pharmacodynamic analysis revealed a small correlation between the steady-state plasma concentration and the percentage of change in WBC and platelet count. The correlation coefficients for these associations were 0.23 and 0.27, respectively.

Discussion

Currently, the primary use of hydroxyurea is as initial therapy in the treatment of myeloproliferative disorders, particularly chronic myelogenous leukemia and polycythemia rubra vera [13, 19]. Hydroxyurea has also been extensively evaluated in solid tumors, with some activity being documented in melanoma, squamous-cell carcinoma of the head and neck, renal-cell carcinoma, and transitional-cell carcinoma [2, 8]. The response rates in these malignancies are low, and hydroxyurea is not part of the standard chemotherapy for any solid tumor. Hydroxyurea is also used in the treatment of advanced cervical carcinoma, where randomized studies have shown an increase in response and survival with concurrent radiotherapy [12, 17], presumably due to inhibition of the repair of radiation-induced DNA damage [21].

On the present trial the MTD of hydroxyurea given over 24 h was a bolus of 1,690 mg/m^2 followed by an infusion of 13,520 mg/m^2. The toxicity at this dose was minimal with a single episode of grade 3 neutropenia being observed in a heavily pretreated patient. A total of ten courses of therapy were given at this dose level without the occurrence of any further episodes of grade 3 toxicity of any type. Thus, this dose level is safe and generally well tolerated. Over 48 h the MTD was a bolus of 2,197 mg/m^2 with an infusion of 17,576 mg/m^2. Although this dose level met the criteria for defining the MTD, its safety is less clearly established than the 24-h MTD. Two of the six patients treated at this dose level had $\geq$ grade 3 hematologic toxicity. In addition, two patients initially treated at the higher dose level who required a dose reduction and were treated at this level developed grade 3 leukopenia. Two patients initially treated at the MTD were subsequently given reduced doses (bolus, 1,690 mg/m^2; infusion, 13,520 mg/m^2) and had episodes of grade 3 or greater toxicity associated with three of five courses at this level. Whether this represents an increase in cumulative toxicity due to prolonged exposure on the 48-h infusion schedule or simply the effect of incomplete recovery is unclear.

A 1 m*M* concentration of hydroxyurea will inhibit DNA synthesis in most mammalian cell lines [16, 20] and is 100 times the concentration required to inhibit synthesis in L1210 cells [14]. The pharmacokinetic analysis done in the present trial shows that steady-state concentrations considerably higher than 1 m*M* can be achieved with tolerable toxicity and low interpatient variability. Continuous infusion hydroxyurea therefore seems likely to provide a more effective and consistent depletion of deoxynucleotide pools, since this effect is dependent on both the dose intensity and the duration of exposure to hydroxyurea.

This study demonstrates that intravenous hydroxyurea can be given safely at high doses as a 24- or 48-h continuous infusion. The recommended phase II doses of this agent are 1,690 mg/m^2 as a bolus followed by 13,520 mg/m^2 as a continuous infusion over 24 h, and 2,197 mg/m^2 as a bolus and 17,576 mg/m^2 as a continuous infusion over 48 h. Further trials are currently being planned.

Acknowledgements. We would like to acknowledge the support of Bristol-Myers/Squibb for providing hydroxyurea for intravenous use and the contributions of Miriam Rogers, R.N., M.S.N., for management of the protocol and Queen Harris for management of the data.

References

1. Akerblom L, Ehrenberg A, Graslund A, Lankinen H, Reichard P, Thelander L (1981) Overproduction of the free radical of ribonucleotide reductase in hydroxyurea-resistant mouse fibroblast 3T6 cells. Proc Natl Acad Sci USA 78: 2159
2. Ariel IM (1970) Therapeutic effects of hydroxyurea: experience with 118 patients with inoperable solid tumors. Cancer 25: 705
3. Beal SL, Boeckmann AJ, Sheiner LB (1989) NONMEM users guide. VI. PREDPP guide. Technical report, University of California, San Francisco
4. Beal SL, Sheiner LB (1989) NONMEM users guide. I. Users basic guide. Technical report, University of California, San Francisco
5. Belt RJ, Haas CD, Kennedy J, Taylor S (1980) Studies of hydroxyurea administered as a continuous infusion: toxicity, pharmacokinetics, and cell synchronization. Cancer 46: 455
6. Bianchi B, Pontis E, Reichard P (1986) Changes of deoxyribonucleoside triphosphate pools induced by hydroxyurea and their relation to DNA synthesis. J Biol Chem 261: 16037
7. Cantwell BMJ, Veale D, Rivett C, Ghani S, Harris AL (1989) Cisplatin with high-dose infusions of hydroxyurea to inhibit DNA repair: a phase II study in non-small-cell lung cancer. Cancer Chemother Pharmacol 23: 252
8. Carter SK, Wasserman TH (1975) The chemotherapy of urologic cancer. Cancer 36: 729
9. Donehower RC (1990) Hydroxyurea. In: Chabner BA, Collins JM (eds) Cancer chemotherapy: principles and practice, 2nd edn. J.B. Lippencott, Philadelphia, p 225
10. Fabricius E, Rajewsky MF (1971) Determination of hydroxyurea in mammalian tissues and blood. Rev Eur Etudes Clin Biol 16: 679
11. Ford SS, Shackney SE (1977) Lethal and sublethal effects of hydroxyurea in relation to drug concentration and duration of drug exposure in sarcoma 180 in vitro. Cancer Res 37: 2628
12. Hreshchyshyn MM, Aron BS, Boronow RC, Franklin EW, Shingleton HM, Blessing JA (1987) Hydroxyurea or placebo combined with radiation to treat stages IIIB and IV cervical cancer confined to the pelvis. Int J Radiat Oncol Biol Phys 5: 317
13. Kennedy BJ (1972) Hydroxyurea therapy in chronic myelogenous leukemia. Cancer 29: 1052
14. Matsumoto M, Rey DA, Cory JG (1990) Effects of cytosine arabinoside and hydroxyurea on the synthesis of deoxyribonucleotides and DNA replication in L1210 cells. Adv Enzyme Regul 30: 47
15. Moran RE, Straus MJ(1979) Cytokinetic analysis of L1210 leukemia after continuous infusion of hydroxyurea in vivo. Cancer Res 39: 1616
16. Pfeiffer SE, Tolmach LJ (1967) Inhibition of DNA synthesis in HeLa cells by hydroxyurea. Cancer Res 27: 124
17. Piver MS, Vongtama V, Emrich LJ (1987) Hydroxyurea plus pelvic radiation versus placebo plus pelvic radiation in surgically staged stage IIIB cervical cancer. J Surg Oncol 35: 129
18. Rosner F, Rubin H, Parise F (1971) Studies on the absorption, distribution, and excretion of hydroxyurea (NSC-32065). Cancer Chemother Rep 55: 167
19. Sharon R, Tatarsky I, Ben-Arieh Y (1986) Treatment of polycythemia vera with hydroxyurea. Cancer 57: 718
20. Sinclair WK (1967) Hydroxyurea: effects on Chinese hamster ovary cells grown in culture. Cancer Res 27: 297
21. Snyder RD (1988) Consequences of depletion of cellular deoxynucleoside triphosphate pools on the excision-repair process in cultured human fibroblasts. Mutat Res 200: 193
22. Veale D, Cantwell BMJ, Kerr N, Upfold A, Harris AL (1988) Phase I study of high-dose hydroxyurea in lung cancer. Cancer Chemother Pharmacol 21: 53